Renal Involvement by Chronic Myelomonocytic Leukemia Requiring Nephroureterectomy

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Chronic monomyelocytic leukemia (CMML) is a relatively rare clonal hematologic disorder with features of myelodysplastic syndrome and myeloproliferative disease. Renal impairment from CMML is infrequent and can result from both direct (ie, infiltrative) and indirect (eg, vasculitis, infarction) mechanisms. This case report describes a patient with refractory gross hematuria requiring nephroureterectomy with diffuse involvement of the upper tract by CMML and accompanying extramedullary hematopoiesis. Underscored are the need to maintain a broad differential diagnosis for upper tract lesions in the setting of gross hematuria, and the potential need for drastic measures to control upper tract bleeding if conservative measures fail.
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Chronic monomyelocytic leukemia (CMML) is a hematologic malignancy considered a subcategory of myelodysplastic syndrome (MDS)/myeloproliferative disease (MPD). The clinical course is variable, but the majority of patients present with fatigue, weight loss, fever, and night sweats. Extramedullary leukemic involvement is rarely a presenting feature of CMML, and direct involvement of the kidney and ureter is also unusual. We present the case of a 70-year-old man with transfusion-dependent MDS who presented with intractable gross hematuria requiring nephroureterectomy. Pathologic analysis revealed CMML involvement

of the renal parenchyma with associated extramedullary hematopoiesis.

Case Report

A 70-year-old Guyanese man with a history of transfusion-dependent MDS, interstitial lung disease, diabetes mellitus, and prostate cancer status-post radical retropubic prostatectomy in 2000 was transferred to our institution with refractory gross hematuria. Four weeks earlier he had developed severe gross hematuria and was admitted to an outside hospital. Computed tomographic urogram revealed enhancement of the right collecting system and extensive clot in the right renal pelvis, ureter, and bladder (Figure 1A, B). Cystoscopy revealed diffuse clot in the bladder, and right ureteroscopy failed secondary to poor visualization. Results on bladder urine acid-fast bacilli test (AFB) and cytology were negative. The patient's bleeding persisted, and he was transferred to our institution.

The patient's medications included metformin, esomeprazole, and prednisone. He had no known drug allergies, was a nonsmoker, and formerly worked as a carpenter. The family history was unremarkable. He had recently traveled to South America.

On presentation, the patient, an elderly man in no acute distress, was afebrile and hemodynamically stable. Results on his physical examination were unremarkable, and he was voiding light blood-tinged urine. Laboratory values included serum creatinine 1.6 mg/dL, white blood cell (WBC) count 27.0 $\times$ 10^9/L, hematocrit 28.7%, platelet count 259 $\times$ 10^9/L, prothrombin time 14.4 seconds, international normalized ratio 1.21, partial thromboplastin time 25.2 seconds, and urinalysis with more than 100 red blood cells and 11 to 25 WBC with subsequent negative urine culture.

On hospital day 1, magnetic resonance imaging (MRI) with contrast demonstrated clot in the right collecting system, enhancement of the right renal pelvis, and mild-to-moderate right hydroureteronephrosis to the level of the bladder. Results on purified protein derivative test were negative. The patient required initiation of continuous bladder irrigation (CBI) and packed red blood cell transfusion.

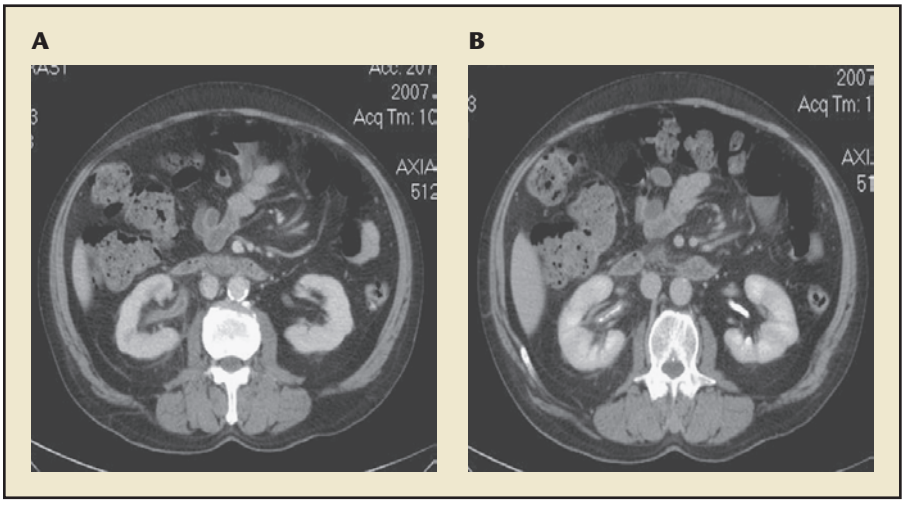
On hospital day 5, the patient was taken for cystoscopy, clot evacuation, and ureteroscopy. Diffuse clot was irrigated from the bladder. Multiple bullous lesions in the bladder were biopsied and fulgurated. Retrograde pyelogram revealed moderate right hydroureteronephrosis with filling defects in the ureter and pelvis. Ureteroscopy revealed inflamed renal pelvis mucosa; however, visualization was limited secondary to large clots filling portions of the collecting system. Washings were sent for cytology, AFB, and culture. Multiple biopsies were taken, and a double-J ureteral stent was placed. Pathologic analysis revealed urothelial tissue with hemorrhage and focal chronic inflammation.

The patient had an uneventful postoperative course, was draining clear urine, and was discharged home. Hematologic consultation revealed no coagulation disorders.

One week later the patient was readmitted to the hospital with recurrent gross hematuria. Renal MRI/magnetic resonance angiography showed improved right hydroureteronephrosis and no vascular malformation or fistula. The patient's bleeding persisted despite CBI and repeated transfusion therapy, and he was taken for laparoscopic right nephroureterectomy on hospital day 4. Postoperative oozing continued from the bladder cuff site, requiring transurethral fulguration on postoperative day 2. On postoperative day 4, decreasing hematocrit prompted a computed tomography scan that revealed retroperitoneal hematoma and significant blood in the subcutaneous tissues; thus, re-exploration through the kidney extraction site was performed and was negative for active bleeding.

Pathologic evaluation of the right kidney and ureter revealed kidney and ureter with marked luminal hemorrhage in the ureter. The sections showed extramedullary hematopoiesis (EMH) in the renal parenchyma extending into

Figure 1. **(A)** *Computed tomography with intravenous contrast demonstrating thickening and enhancement of the right renal pelvis.* **(B)** *Computed tomography with intravenous contrast (delayed image) demonstrating thickened upper tract urothelium and blood clots in the collecting system.*



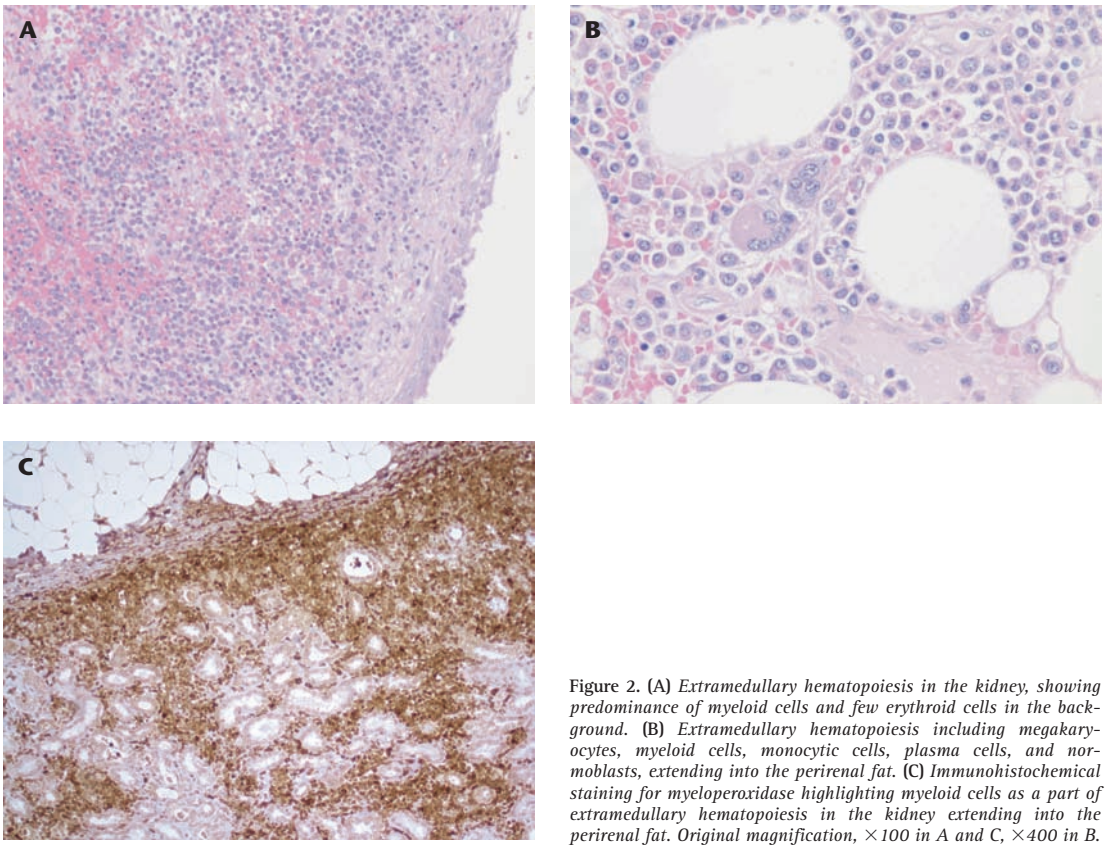


Figure 2. (A) *Extramedullary hematopoiesis in the kidney, showing predominance of myeloid cells and few erythroid cells in the background.* (B) *Extramedullary hematopoiesis including megakaryocytes, myeloid cells, monocytic cells, plasma cells, and normoblasts, extending into the perirenal fat.* (C) *Immunohistochemical staining for myeloperoxidase highlighting myeloid cells as a part of extramedullary hematopoiesis in the kidney extending into the perirenal fat. Original magnification, ×100 in A and C, ×400 in B.*

the perirenal fat (Figure 2A-C). The infiltrate was composed predominantly of left-shifted myeloid and monocytic precursors (highlighted by immunohistochemical stains for myeloperoxidase and lysozyme) and dysplastic megakaryocytes and normoblasts. Few scattered lymphoblasts (CD34+, CD117+) were present within the infiltrate, without evidence of discrete aggregates. Admixed within the infiltrate were polytypic plasma cells and lymphocytes. These findings are characteristic of the involvement of the renal parenchyma and the ureter by CMML. A follow-up bone marrow biopsy showed a hypercellular marrow for age with myeloid hyperplasia and erythroid and megakaryocytic hypoplasia with megakaryocytic dysplasia. The above-mentioned bone marrow findings—increased WBC count (17.7×10^3/uL), persistent absolute monocytosis (16%, 2.8×10^3/uL), transfusion-dependent anemia, mild splenomegaly, and subsequent cytogenetic abnormalities including trisomy 8—were consistent with the final diagnosis of MDS/MPD.

The patient was treated with hydroxyurea and had clear urine and a stable hematocrit. Six months postoperatively, he has not had recurrence of hematuria.

Discussion

This case involved a patient with a history of MDS who developed intractable upper urinary tract bleeding and ultimately required nephroureterectomy. Pathologic analysis revealed diffuse CMML involvement of the right kidney and ureter, with associated extramedullary hematopoiesis.

CMML is a clonal hematologic disorder with features of both MDS and MPD.[1] It is a relatively rare neoplastic disorder and has a heterogeneous clinical course. The diagnosis is characterized by peripheral monocytosis ($>1 \times 10^9$/L), absence of Philadelphia chromosome and *BCR/ABL* fusion gene, fewer than 20% lymphoblasts in the blood or bone marrow, and dysplasia involving 1 or more myeloid lineages.[1] The presentation can range from mild leukocytosis/monocytosis to rare organ involvement, including splenomegaly and lymph node or skin infiltration.[2-4] Extramedullary sites of disease have included skin, lymph nodes, spleen, prostate, and pleura/pericardium.[5-8] There are 6 case reports of CMML causing renal impairment, although direct involvement of the kidney is rare.[9-11] Genitourinary involvement may present as renal failure or gross hematuria,[11,12] renal or perirenal hemorrhage secondary to associated vasculitis,[4] or renal infarction secondary

to blast crisis.[13] Autoimmune phenomena including vasculitis may occur in association with CMML, although this association is poorly understood.[4,14] Our patient presented with gross hematuria leading to obstructive uropathy and hydroureteronephrosis, with intractable symptoms eventually requiring nephroureterectomy.

A similar case report by Bane and colleagues[11] describes a patient presenting with gross hematuria and right flank pain; subsequent nephrectomy revealed CMML involvement of the kidney. Although the patient had no previous hematologic disease, he ultimately developed renal failure and died of sepsis.

EMH was present in proximity to CMML in our patient. EMH can be commonly seen in association with chronic myeloproliferative disorders and results from compromise of intramedullary hematopoiesis and/or severe anemia.[15] Although EMH typically occurs in the reticuloendothelial system (ie, liver, spleen, and lymph nodes), it can rarely occur in other organs, including the adrenal gland, lung, gastrointestinal tract, skin, breast, and central nervous system.[16-19] Renal EMH is unusual in the absence of splenomegaly and hepatomegaly.[11,15,20,21]

This patient's initial differential diagnosis included malignancy (eg, transitional cell carcinoma), infection (eg, granulomatous disease), or another inflammatory process. Enhancement of the urothelium and refractory bleeding were consistent with malignancy. Ureteroscopy was performed twice for the purpose of tissue diagnosis but was limited secondary to poor visualization. Results on repeat urine AFB from the bladder and right ureter were negative to exclude tuberculosis, given the patient's immigrant status and recent travel. Thereafter nephroureterectomy was performed as a last resort for treatment of bleeding and for extirpation of possible malignancy.

This patient required 2 additional procedures after nephroureterectomy for treatment of persistent bleeding, including cystoscopy/fulguration and exploration of the surgical wound, though no active bleeding was found on the second procedure. An associated coagulopathy due to underlying MDS likely exacerbated both bleeding related to the leukemic infiltration and postoperative bleeding that required repeated interventions. However, no specific coagulopathy was found on initial hematologic evaluation.

Although extramedullary hematopoiesis typically occurs in the reticuloendothelial system (ie, liver, spleen, and lymph nodes), it can rarely occur in other organs.

Conclusions

CMML is a relatively rare clonal hematologic disorder with features of both MDS and MPD. Renal impairment from CMML is infrequent and can result from both direct (ie, infiltrative) and indirect (eg, vasculitis, infarction) mechanisms. This case report describes a patient with refractory gross hematuria requiring nephroureterectomy with diffuse involvement of the upper tract by CMML and accompanying EMH. Underscored are the need to maintain a broad differential diagnosis for upper tract lesions in the setting of gross hematuria, and the potential need for drastic measures to control upper tract bleeding if conservative measures fail. ■

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Main Points

- Chronic monomyelocytic leukemia (CMML) is a hematologic malignancy considered a subcategory of myelodysplastic syndrome/myeloproliferative disease.
- The clinical course of CMML is variable, but the majority of patients present with fatigue, weight loss, fever, and night sweats.
- Renal impairment from CMML is infrequent and can result from both direct (ie, infiltrative) and indirect (eg, vasculitis, infarction) mechanisms.
- A broad differential diagnosis for upper tract lesions should be maintained in the setting of gross hematuria.

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